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(57) Abstract

The use of nitric oxide synthase inhibitor in combination with a cytokine-releasing anti-cancer agent for the treatment of cancer or reducing the tumor burden, and pharmaceutical formulations comprising such a combination is disclosed.

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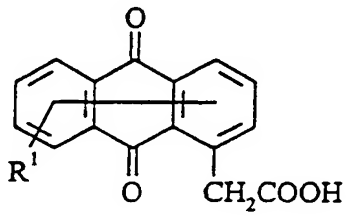
PHARMACEUTICAL COMPOSITIONS CONTAINING NITRIC OXIDE SYNTHASE INHIBITORS AND ANTI-CANCER AGENTS

The present invention relates to the use of a nitric oxide synthase inhibitor in combination with an anticancer agent for the treatment of cancer.

European Patent Application 0278176 discloses a class of xanthenone-4-acetic acid derivatives of formula (I)



(I)

wherein R^1 represents up to two of the groups lower alkyl, halogen, phenyl, CF_3, CN, NO_2, NH_2, CH_2COOH, OR^2, OH, $NHCOR^2$, $NHSO_2R^2$, SR^2, SO_2R^2, CH_2CONHR^2, or NHR^2 (where R^2 is lower alkyl optionally substituted with hydroxy, amino or methoxy functions), at any of the positions 1-8 which are available, R^1 may also represent the substitution of an aza (-N=) group for one or two of the methine (-CH=) groups in the carbocyclic rings and two of R^1 on any two available adjacent poistions may also represent the grouping -CH=CH-CH=CH- to form an additional fused benzene ring; and basic salts thereof, which have anti-tumour properties. 5,6-Dimethylxanthenone-4-acetic acid (DMX) is specifically disclosed.

It has been shown that anti-tumour agents of formula (I) induce tumour haemorrhagic necrosis and elevate plasma nitrate concentrations *(Baguley et al., "Biology of Nitric Oxide, Part II, Enzymology, Biochemistry and Immunology" (Eds. Moncada S, Marletta MA, Hibbs Jr EA), Portland Press, London, 1992, 222-224)*. The greatest increase in plasma nitrate was shown by DMX which also demonstrated the greatest activity against tumours, thus suggesting that nitric oxide production was correlated in some way with the antitumour effects. Furthermore, the inhibition of nitric oxide generation in tumour cell spheroids also inhibited the cytotoxicity induced by DMX. These results strongly implicate nitric oxide produced via the L-arginine pathway as a principal cytotoxic factor (*Thomsen et al., Cancer Chemother. Pharmacol. (1992), 31, 151-155)*. Possible dose-limiting side effects of administering an anti-tumour agent

such as those of formula (I) are the occurrence of deleterious effects of excess nitric oxide generation such as systemic hypotension. It has been confirmed that DMX does indeed increase nitric oxide generation (as assessed by plasma nitrate concentrations) as well as causing hypotension in mice.

However, it has surprisingly been found that administration of an NO synthase inhibitor to tumour-bearing animals treated with a compound of formula (I) does not compromise the anti-tumour effect of the compound of formula (I). This was shown to be the case at doses of the NO synthase inhibitor which completely inhibited the increased nitric oxide generation (as assessed by plasma nitrate concentrations) and caused substantial increases in blood pressure. Therefore, an NO synthase inhibitor can be used to reverse the systemic hypotension without preventing the anti-cancer effect of cytokine-releasing anti-cancer agents.

Accordingly the present invention provides the use of a nitric oxide synthase inhibitor in combination with a cytokine-releasing anti-cancer agent for the manufacture of a medicament for the treatment of cancer in a mammal. Another aspect provides a method of treatment of cancer which comprises administering to a mammal in need thereof an effective amount of a nitric oxide synthase inhibitor in conjunction with a cytokine-releasing anti-cancer agent, and optionally in combination with a further therapeutic agent.

The pharmaceutical combination disclosed by the present invention is also of use in inhibiting or reducing the tumour burden in cancer patients. In particular the pharmaceutical combination of the present invention is of use against solid tumours.

Suitable nitric oxide synthase inhibitors include arginine or amidine analogues, such as those described in US Patent 5028627 or PCT application WO93/13055, for example N^G-monomethyl-L-arginine (L-NMMA) or L-N-iminoethyl-ornithine (L-NIO); and isothiourea derivatives, such as those described in PCT application WO94/12165.

By the term "a cytokine-releasing anti-cancer agent" is meant a compound which, when administered to a mammal, causes a release of cytokines in the body, which give the cytotoxic activity. Examples of cytokines include IL-1, IL-6, TNF-α and IFN-γ.

Suitably, the anti-cancer agents are those compounds within the scope of formula (I) hereinbefore defined, and preferably is DMX.

The present invention is also intended to include nitric oxide synthase inhibitors and anti-cancer agents in the form of salts. Suitable salts include those formed with both organic and inorganic acids. Such acid addition salts will normally be pharmaceutically acceptable although salts of non-pharmaceutically acceptable salts may be of utility in the preparation and purification of the compound in question. Thus, preferred salts, include those formed from hydrochloric, hydrobromic, sulphuric, citric, tartaric, phosphoric, lactive, pyruvic, acetic, succinic, oxalic, fumaric, maleic, oxaloacetic, methanesulphonic, ethanesulphonic, p-toluenesulphonic, benzenesulphonic and isethionic acids.

The nitric oxide synthase inhibitor of the present invention may be administered before, concurrently with or after administration of the anti-cancer agent. Suitably the nitric oxide synthase inhibitor is administered concurrently with or after the anti-cancer agent.

When the nitric oxide synthase inhibitor and anti-cancer agent are administered concurrently, the two separate agents may either be combined and given as a single administration, or may be kept separate and given sequentially.

Whilst it may be possible for the nitric oxide synthase inhibitors and anti-cancer agents to be administered as the raw chemical, it is preferable to present them as a pharmaceutical formulation. Accordingly, a further aspect of the present invention provides a pharmaceutical formulation comprising a nitric oxide inhibitor and/or an anti-cancer agent or pharmaceutically acceptable salts or solvates thereof, together with one or more pharmaceutically acceptable carriers therefor, and optionally one or more other therapeutic agents. The carrier(s) must be "acceptable" in the sense of being compatable with the other ingredients of the formulation and not deleterious to the recipient thereof.

The formulations include those suitable for oral, parenteral (including subcutaneous, intradermal, intramuscular, intravenous and intraarticular), rectal and topical (including dermal, buccal, sublingual and intraocular) administration although the

most suitable route may depend upon for example the condition and disorder of the recipient. The formulations may conveniently be presented in unit dosage form and may be prepared by any of the methods well known in the art of pharmacy. All methods include the step of bringing into association the NO-synthase inhibitor or a pharmaceutically acceptable salt or solvate thereof ("active ingredient") with the carrier which constitutes one or more accessory ingredients. In general the formulations are prepared by uniformly and intimately bringing into association the active ingredient with liquid carriers or finely divided solid carriers or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as a solution or a suspension in an aqueous liquid or a non- aqueous liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing in a suitable machine the active ingredient in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, lubricating, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine a mixture of the powdered compound moistened with an inert liquid diluent. The tablets may optionally be coated or scored and may be formulated so as to provide slow or controlled release of the active ingredient therein.

Formulations for parenteral administration include aqueous and non-aqueous sterile injection solutions which may contain anti-oxidants, buffers, bacteriostats and solutes which render the formulation isotonic with the blood of the intended recipient; and aqueous and non-aqueous sterile suspensions which may include suspending agents and thickening agents. The formulations may be presented in unit-dose or multi-dose containers, for example sealed ampoules and vials, and may be stored in a freeze-dried (lyophilised) condition requiring only the addition of the sterile liquid carrier, for example, saline or water-for-injection, immediately prior to use. Extemporaenous

injection solutions and suspensions may be prepared from sterile powders, granules and tablets of the kind previously described.

Formulations for rectal administration may be presented as a suppository with the usual carriers such as cocoa butter or polyethylene glycol.

Formulations for topical administration in the mouth, for example buccally or sublingually, include lozenges comprising the active ingredient in a flavoured basis such as sucrose and acacia or tragacanth, and pastilles comprising the active ingredient in a basis such as glycerin or sucrose and acacia.

Preferred unit dosage formulations are those containing an effective dose, as hereinbelow recited, or an appropriate fraction thereof, of the active ingredient.

It should be understood that in addition to the ingredients particularly mentioned above, the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavouring agents.

The NO synthase inhibitors of the invention may be administered orally or via injection at a dose of from 1 to 300mg/kg per day. When the NO synthase inhibitors are given by injection, this will normally be in the form of an intravenous bolus or by infusion, preferably the latter. The dose range for adult humans is generally from 70mg to 20g/day and preferably 150mg to 2g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of a nitric oxide synthase inhibitor which is effective at such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 200mg.

L-NMMA is preferably administered by injection, conveniently in the form of an infusion so that between 1 and 300 mg/kg of L-NMMA is administered per day. L-NMMA may also be administered by intravenous bolus in which case the maximum dose per bolus is 30mg/kg and preferably 10mg/kg, the total amount of L-NMMA administered by this method in a day will be between 1 and 300 mg/kg.

The anti-cancer agents of the present invention may be administered orally or via injection at a dose of 0.01g to 10g/kg/day. The dose range for adult humans is generally from 0.7g to 700g/day, and preferably 1.5g to 70g/day. Tablets or other forms of presentation provided in discrete units may conveniently contain an amount of the anti-cancer agent which is effective at such dosage or as a multiple of the same, for instance, units containing 5mg to 500mg, usually around 10mg to 200mg.

The dose of the nitric oxide sythase inhibitor and the anti-cancer agent adminstered will vary with the choice of compound. The man skilled in the art would take these factors into account when determining the doses of the compounds to be used.

The present invention will now be described by way of example only.

Example 1

Materials

5,6-dimethyl xanthenone-acetic acid (DMX) was obtained from the Cancer Research Laboratory, School of Medicine, University of Medicine, Auckland, New Zealand, through the courtesy of Professor Bruce Baguley. L-N-iminoethyl-ornithine (L-NIO) was synthesised at Wellcome Research Laboratories, Langley Court, Beckenham, Kent, UK. DMX was prepared immediately prior to injection by dissolving in 5% (w/v) sodium bicarbonate and was protected from light. L-NIO was prepared in phosphate buffered saline (PBS).

Animal Procedures

C57B1/6 mice (Charles River) were housed under constant temperature and humidity with sterile bedding, water and food according to institutional ethical guidelines. Murine colon adenocarcinoma (Colon 38) tumours were implanted s.c.using a trocar, When tumours reached 4-10mm diameter (10-11 days after implantation) the mice were divided into five groups of 10 mice each. Mice from two groups were treated daily with L-NIO 30mg/kg s.c., followed 8 hours later by 100mg/kg s.c. One of these groups also received a single dose of DMX (30mg/kg i.p.) 2 hours after the first dose of L-NIO. The third group received a single dose of DMX (30mg/kg i.p.) alone. The

fourth group received PBS (0.2 ml/mouse, s.c.) twice daily instead of L-NIO, and the fifth group remained untreated.

Tumours were measured immediately prior to dosing and then on every second day throughout the course of the experiment. Tumour volumes were calculated as $0.52a^2b$, where a and b are the minor and major tumour diameters, respectively.

In order to assess nitric oxide generation, tumour-bearing mice (n = 4/group) were also treated with DMX ± L-NIO according to the above described schedule. Twelve hours after dosing (when plasma levels are maximally elevated) the mice were killed, blood collected, and plasma analysed for nitrate concentration using the Griess reaction after reduction of nitrate to nitrite using acid-washed cadmium. Blood was collected from two untreated mice and analysed for nitrate concentration (controls).

Results

Tumour growth results are summarised in tables 1 and 2. Prior to treatment each group had similar mean and median tumour volumes. Six days after treatment with DMX with or without L-NIO, mean and median tumour volumes were less than pretreatment volumes. For the untreated group, and groups treated with L-NIO alone or with PBS, median tumour volumes at day 6 were greater than pretreatment volumes. Tumours had continued to increase in size in the one group (L-NIO alone) in which tumour growth was assessed after 10 days.

Twelve hours after treatment with DMX alone, or DMX + L-NIO, plasma nitrate concentrations were 203±81μM and 24±7μM, respectively. Plasma nitrate concentrations for control mice were 40±10μM.

Conclusion

This experiment suggests that tumour regressions induced by DMX are not inhibited by the nitric oxide synthase inhibitor L-NIO despite the fact that the dose used completely inhibits the increased nitric oxide generation.

Table 1 Mean Tumour Volumes (mm^3; mean ± SEM; n = 10)

Group	Day				
	0	2	4	6	10
DMX	165±28	172 ± 22	124 ± 15	127 ± 25	-[a]
DMX + L-NIO	156 ± 18	253 ± 32	245 ± 39	151 ± 26	-
Untreated	156 ± 24	288 ± 48	339 ± 51	560 ± 105	-
L-NIO	161 ± 23	330 ± 54	404 ± 56	387 ± 63	648 ± 116
PBS	163 ± 24	268 ± 46	357 ± 68	516 ± 107	-

[a] not done

Table 2 Median Tumour Volumes (mm^3; n = 10)

Group	Day				
	0	2	4	6	10
DMX	167	175	115	98	-[a]
DMX + L-NIO	166	271	205	136	-
Untreated	139	278	291	458	-
L-NIO	155	336	460	356	593
PBS	154	259	326	439	-

[a] not done

Example 2

Effect of L-N-iminoethyl ornithine on systemic arterial blood pressure in the anaesthetised rat

Objective

To evaluate the effects of subcutaneous administration of the nitric oxide synthase inhibitor, L-N-iminoethyl ornithine (L-NIO) over a 60 min period on systemic arterial blood pressure in the anaesthetised rat.

Methods

Rats (male, 250-275g) were anaesthetised with pentobarbitone sodium (60 mg kg^{-1} i.p.), the trachea cannulated to facilitate respiration and the right carotid artery cannulated to allow measurement of systemic arterial blood pressure (BP) using a transducer (Elcomatic) and polygraph (Grass Instruments). After allowing resting BP to stabilise, L-NIO (30 mg kg^{-1}) was administered subcutaneously in the flank, in a volume of 1ml kg^{-1}. BP was determined over the subsequent 60 minutes.

Results

As shown in Table I, L-NIO (30 mg kg^{-1} s.c.) increased BP from a resting value of 93 ± 9 mmHg (n=4) over the subsequent 60 minute period.

Table I

Time after administration of L-NIO (minutes)	10	20	30	40	60
ΔBP (mmHg)	28 ± 3 *	41 ± 1 *	41 ± 6 *	19 ± 9	21 ± 11

Effect of L-NIO (30 mg kg^{-1} s.c.) on BP in the anaesthetised rat. Results are shown as increase in BP (ΔBP), at various times following administration of L-NIO, mean ± s.e.mean of 4 experiments, where significant increase from resting value is shown as *$P<0.05$.

Conclusion

These findings indicate that subcutaneous administration of L-NIO in a dose of 30 mg kg^{-1} significantly increased systemic arterial blood pressure within 10 minutes of injection, with a maximal increase of 41 mmHg being observed 20-30 minutes after administration. The BP response returned towards resting levels by 40-60 minutes.

CLAIMS

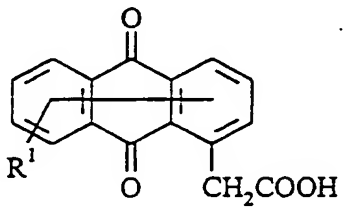
1. The use of a nitric oxide synthase inhibitor in combination with a cytokine-releasing anti-cancer agent for the manufacture of a medicament for the treatment of cancer in a mammal.

2. The use according to claim 1 wherein the cancer is caused by a solid tumour.

3. The use of a nitric oxide synthase inhibitor in combination with a cytokine-releasing anti-cancer agent for the manufacture of a medicament for inhibiting or reducing the tumour burden.

4. The use according to any one of the preceeding claims wherein the nitric oxide synthase inhibitor is an arginine or amidine analogue or an isothiourea derivative.

5. The use according to any one of the preceeding claims wherein the cytokine-releasing anti-cancer agent is a compound of formula (I)



(I)

wherein R^1 represents up to two of the groups lower alkyl, halogen, phenyl, CF_3, CN, NO_2, NH_2, CH_2COOH, OR^2, OH, $NHCOR^2$, $NHSO_2R^2$, SR^2, SO_2R^2, CH_2CONHR^2, or NHR^2 (where R^2 is lower alkyl optionally substituted with hydroxy, amino or methoxy functions), at any of the positions 1-8 which are available, R^1 may also represent the substitution of an aza (-N=) group for one or two of the methine (-CH=) groups in the carbocyclic rings and two of R^1 on any two available adjacent poistions may also represent the grouping -CH=CH-CH=CH- to form an additional fused benzene ring.

6. The use according to claim 5 wherein the anti-cancer agent is 5,6-dimethylxanthenone acetic acid.

7. The use according to any one of the preceeding claims wherein the nitric oxide synthase inhibitor is administered before, concurrently with or after administration of the cytokine-releasing anti-cancer agent.

8. A pharmaceutical combination comprising a nitric oxide synthase inhibitor and a cytokine-releasing anti-tumour agent.

9. A pharmaceutical composition comprising a nitric oxide synthase inhibitor and a cytokine-releasing anti-tumour agent together with one or more pharmaceutically acceptable carriers therefor, and optionally one or more other therapeutic agents.

10. A method for the treatment of cancer comprising administering to a mammal in need thereof an effective amount of a nitric oxide synthase inhibitor in combination with a cytokine-releasing anti-tumour agent.

INTERNATIONAL SEARCH REPORT

Inter ial Application No
PCT/GB 94/02146

A. CLASSIFICATION OF SUBJECT MATTER
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According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EUR J CANCER,, VOL. 29A, NO. 3, PAGE(S) 404-408, 1993 VESZELOVSZKY E et al 'FLAVONE ACETIC ACID AND 5 6 DIMETHYLXANTHENONE-4-ACETIC ACID RELATIONSHIP BETWEEN PLASMA NITRATE ELEVATION AND THE INDUCTION OF TUMOUR NECROSIS' see page 405, column 2, paragraph 2 - page 407, column 2	1-10
X	BIOCHEM PHARMACOL,, VOL. 44, NO. 1, PAGE(S) 192-195, 1992 CHING L-M et al 'STIMULATION OF MACROPHAGE TUMOURICIDAL ACTIVITY BY 5 6 DIMETHYLXANTHENONE-4 ACETIC ACID A POTENT ANALOGUE OF THE ANTITUMOUR AGENT FLAVONE-8-ACETIC ACID'	1-10

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